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Short communication

New polyvinyl chloride membrane electrode without inner reference solution for the determination of methadone

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Abstract

A PVC membrane electrode, without inner reference solution, based on an ion association extraction system responding to methadone (MD) is described. It incorporates a methadone-tetrakis(4-chlorophenyl)borate ion-pair complex in 2-nitrophenyloctyl ether. The prepared electrode exhibits a near Nernstian response (59.5 mV per decade) over the concentration range 2.5×10^{-5}–10^{-1} M MD in solutions of pH 2.0–9.0. The reproducibility of the electrode potentials was ±1 mV by day during at least 6 months. Response time was about 5 s for MD concentrations between 10^{-5} and 10^{-1} M. Determinations of MD in pharmaceutical preparations (tablets and syrups) by direct potentiometry gave an average recovery of 99.3% (w/w) and a mean S.D. of 1.5% (w/w).

Keywords: Ion-selective electrode; Pharmaceutical preparations; Methadone determination

1. Introduction

Methadone hydrochloride (MD HCl) is a powerful narcotic analgesic resembling morphine in its action and use.

There are a variety of methods for the determination of MD, although few of them can readily be adapted to routine analyses as automated monitoring methods for the in-line process control during the production of MD dosage forms. We used liquid chromatography [1–3], gas–liquid chromatography [4,5], gas chromatography [6–10], flow-injection analysis [11], HPLC [12–15], AA–AE spectrometry [16] and potentiometry with ion-selective electrode in our previous work [17].

Although potentiometry presents advantages over the other above-mentioned methods, especially as regards the speed and ease of determination, the characteristics of the electrode used, principally the selectivity and reproducibility of the potentials, resulted in rather inexact results in majority of the cases. The most significant drawback of the selective electrode constructed so far [17] is due to the use of tetraphenylborate as an ion extractor or to the use of a liquid sensor. In effect,

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the electrode, whose construction and evaluation was referred earlier, has a short lifetime in addition to their reduced reproducibility and selectivity.

With a view to obtain an electrode with better operating characteristics than the aforementioned MD electrode [17], tetrakis(4-chlorophenyl)borate was used as an ionic extractor dissolved in 2-nitrophenyloctyl ether. The ion sensor, immobilized in PVC, was applied directly to an epoxy resin support with dispersed graphite as a conductor.

In order to assess the extent of the improvements thus obtained, a detailed study of the operating characteristics was performed and determinations of the primary ion in pharmaceutical preparations commonly available on the local market were conducted.

2. Experimental

2.1. Apparatus and electrodes

A Crison 2002 (sensitivity of ± 0.1 mV) potentiometer, coupled to an electrode switcher of the same brand, was used for measuring the electrode potentials.

All determinations were performed at 25.0 ± 0.2 °C, using a silver chloride–silver Orion 900200 double-junction reference electrode with 0.1 M sodium chloride solution in the outer compartment. An Orion Model 701A digital pH meter was used for the pH measurements.

2.2. Reagents and solutions

The water used in the preparation of all the reagents and standard solutions was doubly deionized. All chemicals were of analytical reagent grade.

The standard 0.01 or 0.1 M aqueous MD HCl solutions were prepared daily by weighing, and when not in use stored away from light.

The buffer used for the potentiometric determination of MD in pharmaceutical preparations was an acetic acid–sodium acetate solution at pH 5.5 and an ionic strength of about 0.1 M, prepared in 1 l flask, by adding 100 ml of a 1 M sodium hydroxide solution to 120 ml of acetic acid and completing the volume with deionized water.

2.3. Membrane preparation and electrode assembly

For the preparation of the membranes, 5 ml of 0.1 M aqueous MD HCl was added to 10 ml of 0.05 M solution of potassium tetrakis(4-chlorophenyl)borate in acetone. The precipitate resulting after evaporating the acetone was filtered and washed with deionized water and dried, protected from the light, in a desiccator at room temperature.

Approximately, 0.04 g of precipitate was dissolved in 0.56 g of 2-nitrophenyloctyl ether. About 0.4 ml of this solution was mixed with 0.18 g of PVC previously dissolved in about 6 ml of tetrahydrofuran, resulting in a membrane whose composition of the ion-pair complex was about 5% (w/w). The prepared membrane was applied directly to a support, composed of a mixture of epoxy resin and graphite.

The constructed electrodes were conditioned by soaking in 5×10^{-3} M MD HCl solution. The same solution was used for conditioning the electrodes, whilst stabilizing the internal potential during the first 3 days after construction.

2.4. Determination of MD in pharmaceutical preparations

For MD HCl determinations in tablets, about 10 tablets were finely powdered and approximately 20 mg of this powder was placed in a 50 ml volumetric flask and diluted with water. For liquids, a volume equivalent to 4 mg of MD HCl was diluted to 50 ml with water.

The potentiometric determinations were performed on these solutions by mixing equal volumes with acetic acid–sodium acetate buffer (pH 5.5 and ionic strength 0.1 M). These measurements were preceded by the calibration of the electrode with solutions of several concentrations of MD HCl standard with the same amount of buffer. The accuracy of the potentiometric determinations was checked by evaluating the recovery. For this, a small amount of MD HCl (500 μl) was added to one sample prepared as previously described. The

variation reading was recorded and used to calculate the percentage recovery of the amount added.

3. Results and discussion

3.1. Electrode behaviour

The overall electrode operating characteristics were assessed on the basis of the calibration curves obtained by measuring the e.m.f. values of a series of MD HCl solutions. The experiments were performed over the concentration range 10^{-1}–10^{-6} M in solutions with (sodium chloride 0.1 M) and without the ionic strength adjusted and in acetic acid–sodium acetate buffer solutions with a pH of 5.5 (Fig. 1).

Table 1 shows the values obtained for the general operating characteristics of the MD electrode under the aforementioned experimental conditions. The data presented correspond to the average of six values obtained in two determinations with three electrodes. Comparing the results obtained with those presented by the previous work for electrode sensitive to the same cationic species using tetraphenylborate as the ionic extractor [17], a significant increase in the linear response range (of about 1 decade of concentration) was noted.

The response time of the electrode was fast, being nearly instantaneous in solutions with pH and the ionic strength adjusted with the setting of a value of ±0.2 mV for the stabilization of the electrode. When the ionic strength was not adjusted, the response of the electrode did not exceed 20 s, when the criterion for its stability was the same.

The values obtained for this parameter are considerably shorter than those referred in the previous work for MD-selective electrode [17], for which response times of about 10 s for concentrations greater than 10^{-3} M and of 90 s for lower values have been claimed. The electrode was washed several times with bidistilled water and

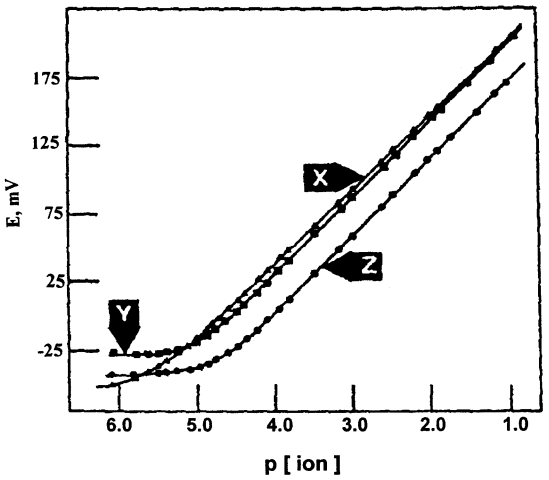

Fig. 1. Calibration curves for MD electrode obtained in solutions: (X) without ionic strength adjusted; (Y) with ionic strength adjusted (NaCl 0.1 M); (Z) in acetic acid–sodium acetate buffer (pH 5.5).

Table 1
Working characteristics for MD-selective electrode

Characteristics	I[a]	II[b]	III[c]
Slope (mV per decade)	55±1	56±0.5	58±0.4
LLLR (M)	7×10^{-6}	3×10^{-5}	9×10^{-5}
LLD (M)	3×10^{-6}	2×10^{-5}	1×10^{-5}
Range of pH[d]	2.0–9.0	2.0–9.0	2.0–9.0
Response time(s)	<20	~5	~5
Reproducibility (mV per day)	±1.3	±1.1	±0.8
Lifetime (months)	>5	>5	>5

[a] Obtained in pure solutions without the ionic strength adjusted.
[b] Obtained in solutions with $\mu = 0.1$ M adjusted with NaCl.
[c] Obtained in acetic acid–sodium acetate buffer solutions (pH 5.5 and $\mu = 0.1$ M).
[d] Obtained in 5×10^{-3} M MD HCl solutions.

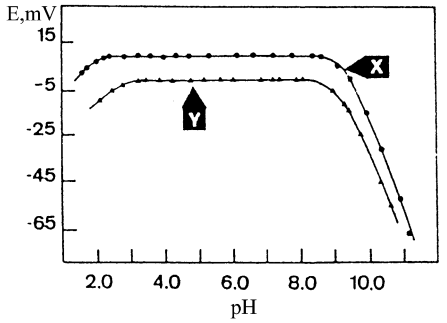

Fig. 2. Effect of pH on the potential of MD electrode in 5×10^{-3} M MD solutions: (X) with ionic strength adjusted to 0.1 M; (Y) without ionic strength adjusted.

kept dry in an opaque closed vessel and stored in a refrigerator while not in use.

3.2. Effect of pH

The effect of pH on the potential of the MD electrode was checked by recording the e.m.f. of the ion-selective electrode in 5×10^{-3} M MD HCl solutions. The pH of the initial solution was modified by adding very small volumes of concentrated hydrochloride acid or sodium hydroxide solutions. The diagrams presented in Fig. 2 show that the electrode potentials in 5×10^{-3} M MD solutions were not affected by the pH in the 2.0–9.0 range. The significant decrease of the potential observed above pH 9 is probably due to the increased concentration of the unprotonated amine.

3.3. Selectivity

The interference of various cations was studied by the separate solution method [18] at two concentration levels without ionic strength adjusted (Table 2). Some of the ions were chosen because they represent potentially low-level contaminants in pharmaceutical preparations of MD.

The more common inorganic cations do not interfere with the normal performance of the MD electrode. Soluble drug excipients and diluents such as maltose, glucose, lactose, starch and gelatin binders that are present in some tablets also do not interfere with the electrode response.

Table 2
Potentiometric selectivity coefficients (log k^{pot}) for methadone selective electrode[a]

Interferent	Concentration (M)	
	1×10^{-4}	1×10^{-3}
Calcium	-3.52 ± 0.05	-3.65 ± 0.06
Sodium	-1.52 ± 0.03	-2.30 ± 0.05
Ammonium	-1.22 ± 0.05	-2.15 ± 0.05
Potassium	-1.33 ± 0.04	-2.12 ± 0.04
Papaverine	0.06 ± 0.02	0.63 ± 0.07
Quinidine	0.19 ± 0.03	2.29 ± 0.02
Trazodone	0.13 ± 0.05	0.35 ± 0.02
Furaltadone	0.08 ± 0.12	1.53 ± 0.03

[a] Mean and S.D. of four values obtained with three electrodes.

As regards the alkaloids studied, the electrode is more selective than other units sensitive to the same species [17], and is adequate for the determinations of the pharmaceutical formulations tested herein.

3.4. Lifetime and reproducibility

Various units, which were constructed and subjected to periodic evaluations, remained operational without altering their response characteristics for at least 5 months. This value was obtained by repeating the calibration curves in MD HCl solutions with the ionic strength adjusted to 0.1 M.

During this time, the reproducibility of the potential readings was about ± 1 mV each day, over the entire concentration range. In the first 3 days after the electrode preparation, however, the potential varied from 5 to 10 mV and should not be used for analytical purpose during this period. This time corresponds to the stabilization of the inner reference system [19].

In the previous studies, on the construction of MD electrode [17], lifetimes not exceeding 8 weeks are given for optimum behaviour. The value given in this paper is exceptionally high, on the one hand, due to the use of 2-nitrophenyloctyl ether as a plasticizing agent and, on the other hand, to the elimination of hydrostatic pressure resulting from the absence of an inner reference solution [20].

Table 3
Determination of MD in some pharmaceutical preparations using MD electrode

Preparation[a]	Labelled active ingredients (%, w/w)	MD found (%)[b]	MD recovery (%)[b]
Metasedin (tablet)[c]	9.85	9.12±0.06	98.3±1.5
Eptadone (syrup)[d]	0.18	0.16±0.02	99.6±2.3
Physeptone (syrup)[e]	0.10	0.08±0.03	101.2±1.3

[a] Commercially available dosage forms with names written in Egypt.
[b] Mean and S.D. of six determinations with two electrodes.
[c] Esteve, Spain.
[d] Simes, Italy.
[e] Wellcome, Australia.

3.5. Analytical applications

The assessment of the analytical usefulness of the electrodes constructed and of the advantages of the new improvements was complemented with a study of how they could be applied to the determination of MD in pharmaceutical preparations currently available on the local market.

The determinations were made on various types of samples (tablets and syrups), prepared as described herein. Table 3 gives the mean results obtained with two electrodes on three independent preparations of each lot (mean of six values).

The solid residues resulting from the preparation of the tablets did not affect the measurements, hence one can dispense with their elimination by filtration.

The values obtained varied between 98.3 and 101.2%, which corresponds to an average recovery of 99.3% and a mean S.D. of 1.5%. This method is being well compared with the British Pharmacopoeia method [21] in which MD can be determined by titrimetric method (0.300 g per 50 ml).

4. Conclusions

The results presented herein led us to conclude that the use of tetrakis(4-chlorophenyl)borate, as an ion extractor, provides electrodes with good operating characteristics, particularly as regards linear range, selectivity and stability.

The elimination of the inner reference solution and the use of 2-nitrophenyloctyl ether as a mediator solvent contributed to the greater reproducibility of the units as compared with other described [17] and most especially to a considerably significant increase in the lifetime of the electrodes.

It is inferred that the electrode based on MD-tetrakis(4-chlorophenyl)borate as an ion exchanger and 2-nitrophenyloctyl ether as mediator, without an inner reference solution, provides a rapid, sensitive, inexpensive and reliable method for MD determinations in pharmaceutical analysis with minimal sample pre-treatment. It is also as good as the procedure described before by Alcada et al. [22].

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